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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/373,403	08/12/1999	WILLIAM R. ARATHOON	P1099C1	2534

23552 7590 12/16/2003

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EXAMINER	
HOLLERAN, ANNE L	

ART UNIT	PAPER NUMBER
1642	28

DATE MAILED: 12/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/373,403	ARATHOON ET AL.	
	Examiner	Art Unit	
	Anne Holleran	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 July 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *30-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The amendments filed March 27, 2003 and July 8, 2003 are acknowledged.

Claims 30-49 are pending and examined on the merits.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections/Objections Withdrawn:

3. The objection to the declaration is withdrawn in view of applicants' statement that the second declaration by inventor Arathoon should be disregarded.

4. The rejection of claims 30-49 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the amendment.

5. The rejection of claims 30-32, 37, 40, and 41 under 35 U.S.C. 102(b) as being anticipated by Carter (WO 93/06217; published 4/1993; cited in the IDS) is withdrawn in view of the amendment.

6. The rejection of claims 30, 31, 37, 40, 41 and 42 under 35 U.S.C. 102(b) as being anticipated by Tso (WO 93/11162; published 6/1993; cited in the IDS) is withdrawn in view of the amendment.

7. The rejection of claims 30-42 under 35 U.S.C. 102(e) as being anticipated by Carter (U.S. Patent 5,731,168; issued March 24, 1998; filing date March 1995) is withdrawn in view of the amendment.

8. The rejection of claims 30-49 under 35 U.S.C. 103(a) as being unpatentable over Vaughan (Nature Biotechnology, 14: 309-314, 1996; cited in the IDS) in view of Bosslet (U.S. Patent 5,591,828; issued Jan. 7, 1997; effective filing date of 6/20/1990) and further in view of either Ridgway (Protein Engineering, 9: 617-621, 1996; cited in the IDS), Carter (U.S. Patent 5,807,706; issued September 15, 1998; effective filing date of March 1, 1995) or Carter (WO 96/27011; published September 1996; cited in the IDS) is withdrawn upon further consideration that this combination of references fails to provide the motivation for choosing two antibodies that happen to both share a light chain for the production of a bispecific antibody.

Claim Rejections/Objections Maintained:

9. The specification continues to be objected to because the newly provided pages of the tables have margins that are too small to accommodate the whole punching. Therefore, text is missing from all pages of the tables.

New Grounds of Rejection:

10. Claim 48 is objected to because it appears to contain a typographical error where "C_H3 domain" is incorrectly set forth as "C,3 domain". Correction is required.

11. Claims 30-42 are rejected under 35 U.S.C. 112, first paragraph, because the specification fails to reasonably provide enablement commensurate with the scope of the claimed invention. The specification does not enable one skilled in the art to which the claimed invention pertains, or with which it is most nearly connected, to make and use the full scope of the claimed invention.

Factors to be considered in determining whether undue experimentation would be required to practice the full scope of the claimed inventions are: 1) quantity of experimentation necessary; 2) the amount of direction or guidance presented in the specification; 3) the presence or absence of working examples; 4) the nature of the invention; 5) the state of the prior art; 6) the relative skill of those in the art; 7) the predictability or unpredictability of the art; and 8) the breadth of the claims. See Ex parte Forman, 230 USPQ 546, BPAI, 1986.

The claims are drawn to bispecific antibodies comprising 2 polypeptides, where each polypeptide comprises a heavy chain, light chain and multimerization domain. The light chain of each of the two polypeptides may be identical because the claims recite that either the first or the second polypeptide comprises either a first or second light chain. The first and second light chains must be at least 80 percent identical to each other. Because of the way the claims are drawn, the first and second polypeptides may both comprise the first light chain, or both

comprise the second light chain, or one polypeptide may comprise the first light chain and the other may comprise the second light chain.

The specification confines its examples to how to screen scFv libraries to find antibody pairs that could be used in bispecific scFv constructs where the light chain is identical. The specification fails to teach how to make such bispecific antibodies, and only teaches how to screen an scFv library for the purpose of discovering heavy and light chain pairings, where one light chain binds to two different heavy chains to make a binding domain that binds to different antigens. The specification fails to teach examples where, after finding such a heavy and light chain pairings, the light chain sequence is then altered and then the altered light chain retains the ability to pair with either heavy chain and the resulting binding domains bind antigen.

Minor modifications in the binding domain of an antibody may lead to drastic changes in antigen binding ability. This assertion is supported by the teachings of Rudikoff (Proc. Natl. acad. Sci. USA, 79: 1979-1983, 1982) demonstrating that alteration of even a single amino acid in the CDR of an antibody results in loss of binding affinity. The claimed methods read on methods of making bispecific antibodies where each of the light chains is altered such that sequence identity is only 80 percent of the sequence identity of the original light chain that was found to associate with each of the heavy chains to produce a functioning binding site. Such a change in sequence identity represents many more than one amino acid change in sequence and encompasses changes to CDR amino acids, and CDRs are the domains most responsible for antigen binding. The claimed methods also read on methods of making bispecific antibodies where the light chains are very different from each other in sequence, and while a change that results in 80 percent sequence identity between the to light chains may be found that results in

efficient pairing and the making of a binding site with adequate binding affinity, it is not predictable that these light chains will be interchangeable with both of the heavy chains. Thus, the claimed methods will result in mispairings, which is what the specification teaches the claimed methods are supposed to avoid.

In view of the fact that small changes in amino acid sequences of antibody chains may result in drastic changes in binding affinity and further in view of the fact that the specification does not describe examples using bispecific antibodies comprising light chains that are only 80 percent identical, one of skill in the art would not be enabled to practice the claimed invention at the time the invention was made.

12. Claims 30-42 are rejected under 35 U.S.C. 112, first paragraph, on the grounds that the applicants were not in possession of the claimed inventions at the time of filing, because the disclosure of the specification fails to adequately describe the claimed genus of compounds to be made in the claimed methods and encoded by the nucleic acids of the claimed host cells. The basis for this rejection is that the specification provides examples of bispecific antibodies that are to be made by the claimed methods and encoded by nucleic acids of the claimed host cells, where the light chains of each of the separate antigen binding regions are identical in sequence. Therefore, a claim to methods of making bispecific antibodies where the light chains of each of the antigen binding regions are at least 80% identical in amino acid sequence is not supported by the specification. In the specification at page 21-22, the discussion of "common light chain" involves the contemplation of light chains that are at least 80% identical in amino acid sequence, but these two light chains do not appear to be used in the method of making bispecific

antibodies. Instead, these two light chains appear to be used as templates for the formation of a "common light chain" that will be used in the method of making a bispecific antibody. Therefore, claims that are drawn to methods of making bispecific antibodies or to host cells comprising nucleic acids encoding bispecific antibodies, where the light chains of each of the separate antigen binding regions at least 80% identical in sequence introduce new matter into the specification, and furthermore, are not described in the specification because the examples provided in the specification are not representative of the full scope of the invention

13. Claims 43-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ridgway (Protein Engineering, 9: 617-621, 1996; cited in the IDS), Carter (U.S. Patent 5,807,706; issued September 15, 1998; effective filing date of March 1, 1995) or Carter (WO 96/27011; published September 1996; cited in the IDS), in view of Kostelney (Journal of Immunology, 148: 1547-1553, 1992; cited in the IDS), and further in view of Vaughan (supra).

Claims 43-49 are drawn to methods for making multispecific antibodies, where the light chain is identical of each of the antigen binding regions is identical in amino acid sequence and where the multispecific antibodies comprise multimerization domains.

Any of Ridgeway, Carter (U.S.) or Carter (WO) teach methods for engineering multimerization domains comprising antibody CH3 regions onto polypeptides comprising heavy and light chain variable domains of antibodies for the purpose of making bispecific antibodies (see abstract, page 620, col. 2, fourth full paragraph of Ridgway; abstract of Carter (U.S.); page 6-7 of Carter (WO)). The Knobs and Holes multimerization domain of Ridgway , Carter (U.S.) or Carter (WO) forms an interface in which the interaction is between a cavity of one

multimerization domain and a protuberance of a second multimerization domain. Any of these reference teaches that the use of multimerization domains increases the efficiency of producing correctly paired bispecific antibodies. Ridgeway, Carter (U.S.) or Carter (WO) fail to teach methods of making bispecific or multispecific antibodies where each of the separate antigen binding domains shares a common light chain.

Kostelney also teaches a method for making bispecific antibodies, and teaches a method for improving heterdimerization . Kosteney teaches a method that employs leucine zipper domains for the purpose of increasing yield of correctly paired bispecific antibodies. Additionally, Kostelney teaches that unwanted proteins may still be formed because of matching of different L chains and H chains (see page 1552, 1st col). Therefore, it appears that the prior art appreciated that there were two problems associated with methods for making bispecific antibodies. One problem was the formation of homodimers instead of heterodimers of heavy chains. This problem is addressed by the inclusion of a multimerization domain, as taught by any of Ridgeway, Carter(U.S.) or Carter (WO) or Kostelney. The second problem is the problem of mismatched heavy and light chain pairings, taught by Kostelney.

Vaughan teaches an example of two scFvs where identical light chains are paired with two different heavy chains to bind to two different antigens, DTPA and CEA, and teaches methods for screening for scFvs with desired characteristics.

Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have altered the methods of Ridgway, Carter (U.S.) or Carter (W.O) to include the step of finding a light chain that could be used for each of the binding domains and would pair with two different heavy chains to make two different antigen binding regions. One

would have been motivated to use the method of Vaughn to look for such light chains because of the problem taught by Kostelney that even if antibodies are engineered to improve the heteroligomerization of two different heavy chains, unwanted antibody product may still be formed because of the mismatching of light chains with heavy chains.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

14. Claims 30-49 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 30-51 of copending Application No. 09/863,693. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of application no. 09/863,693 are drawn to methods for making, and host cells comprising nucleic acids encoding, bispecific antibodies, where the method steps and characteristics of the host cells are the same as that in the instant application. Bispecific antibodies are an obvious species of multispecific antibodies.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

15. Claims 30-49 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 47-63 of copending Application No. 09/520,130. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of application no. 09/520,130 are drawn to multispecific antibodies that have the same or similar characteristics to the antibodies made by the claimed methods and host cells of the instant application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

16. Claims 30-49 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-29 of copending Application No. 10/143,437. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of application no. 10/143,437 are drawn to methods of making multispecific antibodies where the multispecific antibodies have a common light chain. Such methods are within the scope of the instant methods are an obvious species.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claim is allowed.

Claims 30-42 are free of the art, because these claims read on bispecific antibodies that are diabodies comprising a multimerization domain, or are two scFvs joined together by a multimerization domain. Whitlow (U.S. 6,515,110, effective filing Nov. 20, 1992, made of record), for example, teaches such antibodies that contain alterations in sequence to improve dimerization, but there does not appear to be any suggestion in the art for making such constructs with light chains that have at least 80 percent sequence identity.

Any inquiry concerning this communication or earlier communications from the Office should be directed to Anne Holleran, Ph.D. whose telephone number is (703) 308-8892. Examiner Holleran can normally be reached Monday through Friday, 9:30 am to 2:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D. can be reached at (703) 308-3995.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist at telephone number (703) 308-0196.

Anne L. Holleran
Patent Examiner
December 13, 2003